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(FILE 'HOME' ENTERED AT 11:43:06 ON 28 FEB 2001)

FILE 'MEDLINE, BIOSIS, SCISEARCH, EMBASE, CAPLUS' ENTERED AT 11:43:27 ON 28 FEB 2001

L1 2131122 S ANTIBODY
L2 284002 S L1 AND RECEPTOR
L3 11913 S L2 AND EPIDERMAL GROWTH FACTOR
L4 6 S L3 AND VEGF PRODUCTION
L5 0 S L4 AND INHIBIT

=> s l1 and EGFR

L6 2954 L1 AND EGFR

=> s l6 and VEGF production

L7 5 L6 AND VEGF PRODUCTION

=> dup remove

ENTER L# LIST OR (END):17

PROCESSING COMPLETED FOR L7

L8 1 DUP REMOVE L7 (4 DUPLICATES REMOVED)

=> d l8 all 1-4

L8 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
AN 93184390 MEDLINE
DN 93184390
TI Epidermal growth factor stimulates vascular endothelial growth factor production by human malignant glioma cells: a model of glioblastoma multiforme pathophysiology.
AU Goldman C K; Kim J; Wong W L; King V; Brock T; Gillespie G Y
CS Brain Tumor Research Laboratories, Division of Neurosurgery, University of Alabama, Birmingham 35294-0006.
NC T32NSO7335 (NINDS)
NS31096 (NHLBI)
HL-41180
SO MOLECULAR BIOLOGY OF THE CELL, (1993 Jan) 4 (1) 121-33.
Journal code: BAU. ISSN: 1059-1524.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199306
AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathologic features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors. By immunoperoxidase and immunofluorescence, we definitively have demonstrated the presence of vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (**EGFr**) in five out of five human glioma cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro experiments with glioma cell lines revealed a consistent and reliable relation between **EGFr** activation and **VEGF production**; namely, EGF (1-20 ng/ml) stimulation of glioma cells resulted in a 25-125% increase in

secretion of bioactive VEGF. Conditioned media (CM) prepared from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concentrations of Ca^{2+} ($[\text{Ca}^{2+}]_i$) in human umbilical vein endothelial cells (HUVECs). Neither EGF alone or CM from glioma cultures prepared in the absence of EGF induced $[\text{Ca}^{2+}]_i$ increases in HUVECs. Preincubation of glioma CM with A4.6.1, a monoclonal **antibody** to VEGF, completely abolished VEGF-mediated $[\text{Ca}^{2+}]_i$ transients in HUVECs. Likewise, induction by glioma-derived CM of von Willebrand factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiology of GBM tumor angiogenesis, increased vascular permeability, and cellular proliferation. Specifically, EGF activation of **EGFr** expressed on glioma cells leads to enhanced secretion of VEGF by glioma cells. VEGF released by glioma cells in situ most likely accounts for pathognomonic histopathologic and clinical features of GBM tumors in patients, including striking tumor angiogenesis, increased cerebral edema and hypercoagulability manifesting as focal tumor necrosis, deep vein thrombosis, or pulmonary embolism.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
 Brain Neoplasms: BS, blood supply
 Brain Neoplasms: PA, pathology
 Brain Neoplasms: PP, physiopathology
 *Endothelial Growth Factors: BI, biosynthesis
 *Epidermal Growth Factor: PD, pharmacology
 Glioblastoma: BS, blood supply
 Glioblastoma: PA, pathology
 Glioblastoma: PP, physiopathology
 *Glioma: ME, metabolism
 Immunohistochemistry
 *Lymphokines: BI, biosynthesis
 Models, Biological
 Neovascularization, Pathologic: PP, physiopathology
 Receptor, Epidermal Growth Factor: ME, metabolism
 Tumor Cells, Cultured: DE, drug effects
 Tumor Cells, Cultured: ME, metabolism

RN 62229-50-9 (Epidermal Growth Factor)

CN EC 2.7.11.- (Receptor, Epidermal Growth Factor); 0 (vascular permeability factor); 0 (Endothelial Growth Factors); 0 (Lymphokines)

LA English
 CC 14-1 (Mammalian Pathological Biochemistry)
 Section cross-reference(s): 2
 AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathol. features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors.
 By immunoperoxidase and immunofluorescence, we have definitively demonstrated the presence of vascular endothelial growth factor (VEGF) and **epidermal growth factor receptor** (EGFr) in five out of five human glioma cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro expts. with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF** **prodn.**; namely, EGF (1-20 ng/mL) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive VEGF. Conditioned media (CM) prepd. from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concns. of Ca^{2+} ($[Ca^{2+}]_i$) in human umbilical vein endothelial cells (HUVECs). Neither EGF alone or CM from glioma cultures prepd. in the absence of EGF induced $[Ca^{2+}]_i$ increases in HUVECs. Preincubation of glioma CM with A4.6.1, a monoclonal **antibody** to VEGF, completely abolished VEGF-mediated $[Ca^{2+}]_i$ transients in HUVECs. Likewise, induction by glioma-derived CM of von Willebrand factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiol. of GBM tumor angiogenesis, increased vascular permeability, and cellular proliferation.
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 ST EGF **receptor** vascular growth factor glioblastoma
 IT **Receptors**
 RL: BIOL (Biological study)
 (**epidermal growth factor**, vascular endothelial growth factor formation stimulation by, in glioblastoma multiforme cells of humans)
 IT Neuroglia
 (neoplasm, glioblastoma multiforme, vascular endothelial growth factor formation in, **epidermal growth factor receptor** stimulation of, in human cells)
 IT 127464-60-2, Vascular endothelial growth factor
 RL: FORM (Formation, nonpreparative)
 (formation of, by glioblastoma multiforme cells of humans, EGF **receptor** stimulation of)
 IT 7440-70-2, Calcium, biological studies
 RL: BIOL (Biological study)
 (influx of, in human umbilical vein endothelial cells, vascular endothelial growth factor stimulation of, glioblastoma multiforme pathogenesis in relation to)
 IT 62229-50-9, **Epidermal growth factor**
 RL: BIOL (Biological study)
 (**receptors** for, of glioblastoma multiforme cells of humans, vascular endothelial growth factor formation stimulation by)

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Files
NEWS 4 Oct 27 SET ABBREVIATIONS and SET PLURALS extended in
Derwent World Patents Index files
NEWS 5 Oct 27 Patent Assignee Code Dictionary now available
in Derwent Patent Files
NEWS 6 Oct 27 Plasdoc Key Serials Dictionary and Echoing added to
Derwent Subscriber Files WPIDS and WPIX
NEWS 7 Nov 29 Derwent announces further increase in updates for DWPI
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biotechnology
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NEWS 15 Jan 05 AIDSLINE is being removed from STN
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NEWS 17 Feb 16 TOXLINE no longer being updated

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NEWS LOGIN Welcome Banner and News Items
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=> s antibody

L1 2131122 ANTIBODY

=> s l1 and receptor

L2 284002 L1 AND RECEPTOR

=> s l2 and epidermal growth factor

L3 11913 L2 AND EPIDERMAL GROWTH FACTOR

=> s l3 and VEGF production

L4 6 L3 AND VEGF PRODUCTION

=> s l4 and inhibit

L5 0 L4 AND INHIBIT

=> d l4 all 1-6

L4 ANSWER 1 OF 6 MEDLINE

AN 93184390 MEDLINE

DN 93184390

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 Brain Neoplasms: PP, physiopathology
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 Models, Biological
 Neovascularization, Pathologic: PP, physiopathology
Receptor, Epidermal Growth Factor: ME, metabolism
 Tumor Cells, Cultured: DE, drug effects
 Tumor Cells, Cultured: ME, metabolism

RN **62229-50-9 (Epidermal Growth Factor)**

CN EC 2.7.11.- (**Receptor, Epidermal Growth Factor**); 0 (vascular permeability factor); 0 (Endothelial Growth Factors); 0 (Lymphokines)

L4 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1993:230726 BIOSIS

DN PREV199395121901

TI **Epidermal growth factor** stimulates vascular endothelial growth factor production by human malignant glioma cells: A model of glioblastoma multiforme pathophysiology.

AU Goldman, Corey K. (1); Kim, Jin; Wong, Wai-Lee; King, Vickie; Brock, Tommy; Gillespie, G. Yancey (1)

CS (1) Brain Tumor Res. Lab., Div. Neurosurg., Dep. Surg., Univ. Ala.
Birmingham, Birmingham, AL 35294-0006

SO Molecular Biology of the Cell, (1993) Vol. 4, No. 1, pp. 121-133.
ISSN: 1059-1524.

DT Article

LA English

AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathologic features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors. By immunoperoxidase and immunofluorescence, we definitively have demonstrated the presence of vascular endothelial growth factor (VEGF) and **epidermal growth factor receptor** (EGFr) in five out of five human glioma cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro experiments with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF production**; namely, EGF (1-20 ng/ml) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive VEGF.

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CC Cytology and Cytochemistry - Human *02508
Clinical Biochemistry; General Methods and Applications 10006
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals 10069
Metabolism - Minerals *13010
Metabolism - Proteins, Peptides and Amino Acids *13012
Cardiovascular System - Blood Vessel Pathology *14508
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Endocrine System - General *17002
Nervous System - Pathology *20506
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines 24005
Neoplasms and Neoplastic Agents - Biochemistry *24006

BC Hominidae *86215

IT Major Concepts
Cardiovascular Medicine (Human Medicine, Medical Sciences); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Hematology (Human Medicine, Medical Sciences); Metabolism; Neurology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences)

IT Chemicals & Biochemicals
CALCIUM ION

IT Miscellaneous Descriptors
 CALCIUM ION CONCENTRATION; CH-235MG CELL LINE; D-54MG CELL LINE;
 D-65MG
 CELL LINE; EMBOLISM; HYPERCOAGULABILITY; SURGICAL SPECIMENS;
 THROMBOSIS; TUMOR ANGIOGENESIS; U-105MG CELL LINE; U-251MG CELL LINE
 ORGN Super Taxa
 Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
 ORGN Organism Name
 Hominidae (Hominidae)
 ORGN Organism Superterms
 animals; chordates; humans; mammals; primates; vertebrates
 RN 14127-61-8 (CALCIUM ION)

L4 ANSWER 3 OF 6 SCISEARCH COPYRIGHT 2001 ISI (R)
 AN 1998:167840 SCISEARCH
 GA The Genuine Article (R) Number: YY117
 TI Vascular endothelial growth factor induces heparin-binding
epidermal growth factor-like growth factor in
 vascular endothelial cells
 AU Arkonac B M (Reprint); Foster L C; Sibinga N E S; Patterson C; Lai K H;
 Tsai J C; Lee M E; Perrella M A; Haber E
 CS HARVARD UNIV, SCH PUBL HLTH, CARDIOVASC BIOL LAB, 677 HUNTINGTON AVE,
 BOSTON, MA 02115 (Reprint); KAOHSIUNG MED COLL, DEPT MED, KAOHSIUNG,
 TAIWAN; HARVARD UNIV, SCH MED, DEPT MED, BOSTON, MA 02115; BRIGHAM &
 WOMENS HOSP, DIV PULM, BOSTON, MA 02115; BRIGHAM & WOMENS HOSP, DIV
 CARDIOVASC, BOSTON, MA 02115
 CYA USA; TAIWAN
 SO JOURNAL OF BIOLOGICAL CHEMISTRY, (20 FEB 1998) Vol. 273, No. 8, pp.
 4400-4405.
 Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE
 PIKE, BETHESDA, MD 20814.
 ISSN: 0021-9258.
 DT Article; Journal
 FS LIFE
 LA English
 REC Reference Count: 50
 AB Although several cytokines and growth factors have been shown to
 regulate vascular endothelial growth factor (**VEGF**)
production, little is known about how VEGF may regulate growth
 factors that have known mitogenic and chemotactic actions on mesenchymal
 cells (which are involved in the maturation of the angiogenic process).
 We investigated the effect of VEGF on heparin-binding **epidermal**
growth factor-like growth factor (HB-EGF) expression in
 human umbilical vein endothelial cells. HB-EGF mRNA was induced by 8-fold
 after 2 h of VEGF stimulation, and it returned to base line within 6 h.
 VEGF did not alter the half-life of HB-EGF mRNA (55 min). Nuclear run-on
 experiments showed a 4.9-fold increase in HB-EGF gene transcription
 within
 2 h of VEGF stimulation, and Western analysis demonstrated an associated
 increase in cellular HB-EGF protein. We found that platelet-derived
 growth
 factor-BB (PDGF-BB) mRNA was also induced 3-fold after 5 h of VEGF
 stimulation, whereas neither endothelin 1 nor transforming growth
 factor-beta 1 was regulated by VEGF. Finally, conditioned medium from
 VEGF-stimulated endothelial cells produced an increase in DNA synthesis
 in
 vascular smooth muscle cells, and this effect was blocked by a
 neutralizing **antibody** to PDGF. The induction of HB-EGF an
 PDGF-BB expression in endothelial cells may represent the mechanism by
 which VEGF recruits mesenchymal cells to form the medial and adventitial
 layers of arterioles and venules during the course of angiogenesis.
 CC BIOCHEMISTRY & MOLECULAR BIOLOGY

STP KeyWords Plus (R): SMOOTH-MUSCLE CELLS; FACTOR MESSENGER-RNA; FACTOR GENE;

ATHEROSCLEROTIC PLAQUES; **RECEPTOR** EXPRESSION; PHORBOL ESTER; ANGIOGENESIS; EGF; HYPOXIA; INDUCTION

RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
=====	+	+	+	=====
ALBERTS G F	1994	269	10112	J BIOL CHEM
BERKMAN R A	1993	91	153	J CLIN INVEST
BLOCH K D	1989	264	10851	J BIOL CHEM
BORNFELDT K E	1994	93	1266	J CLIN INVEST
BREIER G	1992	114	521	DEVELOPMENT
BROGI E	1994	90	649	CIRCULATION
BROGI E	1996	97	469	J CLIN INVEST
CARMELIET P	1996	380	435	NATURE
COHEN T	1996	271	736	J BIOL CHEM
CONNOLLY D T	1989	84	1470	J CLIN INVEST
DAMORE P A	1993	8	61	GROWTH FACTORS
DAMORE P A	1992	3	49	SEMIN CANCER BIOL
DAS S K	1994	120	1071	DEVELOPMENT
DVORAK H F	1995	146	1029	AM J PATHOL
FOLKMAN J	1996	87	1153	CELL
FOLKMAN J	1995	333	1757	NEW ENGL J MED
FONG G H	1995	376	66	NATURE
FREEMAN M R	1995	55	4140	CANCER RES
GIAID A	1995	59	R1308	TRANSPLANTATION
HANAHAN D	1996	86	353	CELL
HIGASHIYAMA S	1992	267	6205	J BIOL CHEM
HIGASHIYAMA S	1991	251	936	SCIENCE
KLASBRUN M	1993	3	699	CURR BIOL
KOOLWIJK P	1996	132	1177	J CELL BIOL
KUZUYA M	1995	164	658	J CELL PHYSIOL
LAZAROUS D F	1996	94	1074	CIRCULATION
LEUNG D W	1989	246	1306	SCIENCE
LEVY A P	1996	271	2746	J BIOL CHEM
LI J	1995	270	308	J BIOL CHEM
LINDAHL P	1997	277	242	SCIENCE
MANDRIOTA S J	1995	270	9709	J BIOL CHEM
MARIKOVSKY M	1993	90	3889	P NATL ACAD SCI USA
MIYAGAWA J	1995	95	404	J CLIN INVEST
MORITA T	1993	197	256	BIOCHEM BIOPH RES CO
NEHLS V	1994	48	349	MICROVASC RES
NEUFELD G	1994	5	89	PROG GROWTH FACTOR R
NICOSIA R F	1995	73	658	LAB INVEST
NOMURA M	1995	270	28316	J BIOL CHEM
OBRIEN E R	1994	145	883	AM J PATHOL
ORLIDGE A	1987	105	1455	J CELL BIOL
PATTERSON C	1995	270	23111	J BIOL CHEM
PEPPER M S	1993	204	356	EXP CELL RES
PERRELLA M A	1994	269	14595	J BIOL CHEM
RAAB G	1994	204	592	BIOCHEM BIOPH RES CO
RUEF J	1997	81	24	CIRC RES
SHALABY F	1995	376	62	NATURE
SHWEIKI D	1992	359	843	NATURE
SURI C	1996	87	1171	CELL
TEMIZER D H	1992	267	24892	J BIOL CHEM
YOSHIZUMI M	1992	267	9467	J BIOL CHEM

L4 ANSWER 4 OF 6 SCISEARCH COPYRIGHT 2001 ISI (R)

AN 93:101700 SCISEARCH

GA The Genuine Article (R) Number: KM253

TI **EPIDERMAL GROWTH-FACTOR** STIMULATES VASCULAR

ENDOTHELIAL GROWTH-FACTOR PRODUCTION BY HUMAN-MALIGNANT GLIOMA-CELLS - A
MODEL OF GLIOBLASTOMA-MULTIFORME PATHOPHYSIOLOGY

AU GOLDMAN C K (Reprint); KIM J; WONG W L; KING V; BROCK T; GILLESPIE G Y
CS UNIV ALABAMA, DEPT SURG, DIV NEUROSURG, BRAIN TUMOR RES LABS, BIRMINGHAM,
AL, 35294 (Reprint); UNIV ALABAMA, DEPT MED, DIV CARDIOVASC SCI, VASC

BIOL

& HYPERTENS PROGRAM, BIRMINGHAM, AL, 35294; GENENTECH INC, S SAN
FRANCISCO, CA, 94080

CYA USA

SO MOLECULAR BIOLOGY OF THE CELL, (JAN 1993) Vol. 4, No. 1, pp. 121-133.
ISSN: 1059-1524.

DT Article; Journal

FS LIFE

LA ENGLISH

REC Reference Count: 47

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CC CYTOLOGY & HISTOLOGY; BIOCHEMISTRY & MOLECULAR BIOLOGY

STP KeyWords Plus (R): PERMEABILITY FACTOR; POSTOPERATIVE THROMBOEMBOLISM;
NEUROSURGICAL PATIENTS; FACTOR-ALPHA; EXPRESSION; **RECEPTOR**;
PROTEIN; ASTROCYTOMAS; PROGRESSION; POLYPEPTIDE

RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
ADACHI K	1992	34	370	CANCER IMMUNOL IMMUN
BAR R S	1989	124	1841	ENDOCRINOLOGY
BETHEA J R	1992	152	264	J CELL PHYSIOL
BETHEA J R	1990	30	1	J NEUROIMMUNOL
BETHEA J R	1992	36	179	J NEUROIMMUNOL
BIGNER D D	1981	40	210	J NEUROPATH EXP NEUR
BIGNER S H	1985	3	769	NEUROL CLIN

BIGNER S H	1984	27	67	PROG EXP TUMOR RES
BLUMENSTOCK M	1991	11	1353	ANTICANCER RES
BOSTROM S	1986	80	83	ACTA NEUROCHIR
BOSTROM S	1987	88	49	ACTA NEUROCHIR
BRADY L W	1991	22	225	INT J RADIAT ONCOL
BROCK T A	1991	138	213	AM J PATHOL
BROCK T A	1988	136	54	J CELL PHYSL
BURGER P C	1987	57	1617	CANCER
BURGER P C	1989	63	2014	CANCER
CHEN T R	1977	104	255	EXP CELL RES
CLAUSS M	1990	172	1535	J EXP MED
CONN G	1990	87	1323	P NATL ACAD SCI USA
CONNOLLY D T	1991	47	219	J CELL BIOCHEM
CONSTANTINI S	1991	109	93	ACTA NEUROCHIR
CRISCUOLO G R	1989	71	884	J NEUROSURG
FERRARA N	1991	47	211	J CELL BIOCHEM
FETT J W	1985	24	5480	BIOCHEMISTRY-US
FOLKMAN J	1972	173	409	ANN SURG
FULLING K H	1984	1	152	SEMIN DIAGN PATHOL
GOSPODAROWICZ D	1987	8	95	ENDOCR REV
GOSPODAROWICZ D	1989	93	S 39	J INVEST DERMATOL
GRYNKIEWICZ G	1985	260	3440	J BIOL CHEM
HICKS C	1989	67	271	IMMUNOL CELL BIOL
ISHIKAWA F	1989	338	557	NATURE
KIM K J	1992	7	53	GROWTH FACTORS
LEUNG D W	1989	246	1306	SCIENCE
MARUNO M	1991	75	97	J NEUROSURG
MAXWELL M	1991	51	1345	CANCER RES
MONREAL M	1991	67	541	CANCER
MURTHY U	1987	252	549	ARCH BIOCHEM BIOPHYS
OHNISHI T	1991	10	13	J NEURO-ONCOL
PONTEN J	1968	74	465	ACTA PATHOL MIC SC
PONTEN J	1978	56	184	MED BIOL
ROBERTS A B	1986	84	4167	P NATL ACAD SCI USA
SANG U H	1989	74	83	J NEUROSURG
SCHREIBER A B	1986	232	1250	SCIENCE
TISCHER E	1991	266	11947	J BIOL CHEM
TUOMELA T	1990	46	1197	LIFE SCI
WIKSTRAND C J	1985	44	229	J NEUROPATH EXP NEUR
ZAGZAG D	1990	50	7393	CANCER RES

L4 ANSWER 5 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 93071308 EMBASE

DN 1993071308

TI **Epidermal growth factor** stimulates vascular endothelial growth factor production by human malignant glioma cells: A model of glioblastoma multiforme pathophysiology.

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SO Molecular Biology of the Cell, (1993) 4/1 (121-133).

ISSN: 1059-1524 CODEN: MBCEEV

CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy
016 Cancer

LA English

SL English

AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathologic features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors. By immunoperoxidase and immunofluorescence, we definitively have demonstrated

the presence of vascular endothelial growth factor (VEGF) and **epidermal growth factor receptor** (EGFr) in five out of five human glioma cell lines (U- 251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro experiments with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF production**; namely, EGF (1-20 ng/ml) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive VEGF.

Conditioned

media (CM) prepared from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concentrations of Ca²⁺ ([Ca²⁺](i)) in human umbilical vein endothelial cells (HUVECs). Neither EGF alone or CM from glioma cultures prepared in the absence of EGF induced [Ca²⁺](i) increases in HUVECs. Preincubation of glioma CM

with

A4.6.1, a monoclonal **antibody** to VEGF, completely abolished VEGF-mediated [Ca²⁺](i) transients in HUVECs. Likewise, induction by glioma-derived CM of von Willebrand factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiology of GBM tumor angiogenesis, increased vascular permeability, and cellular

proliferation.

Specifically, EGF activation of EGFr expressed on glioma cells leads to enhanced secretion of VEGF by glioma cells. VEGF released by glioma cells in situ most likely accounts for pathognomonic histopathologic and clinical features of GBM tumors in patients, including striking tumor angiogenesis, increased cerebral edema and hypercoagulability manifesting as focal tumor necrosis, deep vein thrombosis, or pulmonary embolism.

CT Medical Descriptors:

- *angiogenesis
- *glioblastoma
- *glioma cell
- *pathophysiology

adult

article

calcium cell level

cell proliferation

clinical feature

female

histopathology

human

human cell

tumor cell line

Drug Descriptors:

epidermal growth factor receptor

growth factor receptor

***epidermal growth factor**

*vasculotropin: EC, endogenous compound

RN (epidermal growth factor) 62229-50-9;

(vasculotropin) 127464-60-2

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AN 1993:210425 CAPLUS

DN 118:210425

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SO Mol. Biol. Cell (1993), 4(1), 121-33

CODEN: MBCEEV; ISSN: 1059-1524

DT Journal